

MSC engineered to produce BDNF for the treatment of Huntington's disease

Grant Award Details

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Grant Type: Disease Team Therapy Development - Research

Grant Number: DR2A-05415

Project Objective: Original objective: To develop human MSC engineered with lentivirus to overexpress BDNF as a cell therapy for treatment of Huntington's Disease, including completion of a Phase 1 trial.
Modified objective as of 2015: To complete the PRE-CELL Observational trial of HD patients for 1 year past the last patient in (to July 2016). No longer expect to fund an interventional Phase 1 trial under this award. In addition, the preclinical work led by Jan Nolta was ended as of July 31, 2016.

Investigator:

Name: Vicki Wheelock
Institution: University of California, Davis
Type: PI

Name: Jan Nolta
Institution: University of California, Davis
Type: Co-PI

Disease Focus: Huntington's Disease, Neurological Disorders

Human Stem Cell Use: Adult Stem Cell

Cell Line Generation: Adult Stem Cell

Award Value: \$8,924,235

Status: Closed

Progress Reports

Reporting Period: Year 1

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Reporting Period:	Year 2
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Reporting Period:	Year 3
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Reporting Period:	Year 4/NCE
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Grant Application Details

Application Title: MSC engineered to produce BDNF for the treatment of Huntington's disease

Public Abstract: One in every ten thousand people in the USA has Huntington's disease, and it impacts many more. Multiple generations within a family can inherit the disease, resulting in escalating health care costs and draining family resources. This highly devastating and fatal disease touches all races and socioeconomic levels, and there are currently no cures. Screening for the mutant HD gene is available, but the at-risk children of an affected parent often do not wish to be tested since there are currently no early prevention strategies or effective treatments.

We propose a novel therapy to treat HD; implantation of cells engineered to secrete Brain-Derived Neurotrophic factor (BDNF), a factor needed by neurons to remain alive and healthy, but which plummets to very low levels in HD patients due to interference by the mutant Huntingtin (htt) protein that is the hallmark of the disease. Intrastriatal implantation of mesenchymal stem cells (MSC) has significant neurorestorative effects and is safe in animal models. We have discovered that MSC are remarkably effective delivery vehicles, moving robustly through the tissue and infusing therapeutic molecules into each damaged cell that they contact. Thus we are utilizing nature's own paramedic system, but we are arming them with enhanced neurotrophic factor secretion to enhance the health of at-risk neurons. Our novel animal models will allow the therapy to be carefully tested in preparation for a phase I clinical trial of MSC/BDNF infusion into the brain tissue of HD patients, with the goal of restoring the health of neurons that have been damaged by the mutant htt protein.

Delivery of BDNF by MSC into the brains of HD mice is safe and has resulted in a significant reduction in their behavioral deficits, nearly back to normal levels. We are doing further work to ensure that the proposed therapy will be safe and effective, in preparation for the phase I clinical trial. The significance of our studies is very high because there are currently no treatments to diminish the unrelenting decline in the numbers of medium spiny neurons in the striata of patients affected by HD. Our biological delivery system for BDNF could also be modified for other neurodegenerative disorders such as amyotrophic lateral sclerosis (ALS), spinocerebellar ataxia (SCA1), Alzheimer's Disease, and some forms of Parkinson's Disease, where neuroregeneration is needed. Development of novel stem cell therapies is extremely important for the community of HD and neurodegenerative disease researchers, patients, and families. Since HD patients unfortunately have few other options, the potential benefit to risk ratio for the planned trial is very high.

Statement of Benefit to California:

It is estimated that one in 10,000 CA residents have Huntington's disease (HD). While the financial burden of HD is estimated to be in the billions, the emotional cost to friends, families, and those with or at risk for HD is immeasurable. Health care costs are extremely high for HD patients due to the long progression of the disease, often for two decades. The lost ability of HD patients to remain in the CA workforce, to support their families, and to pay taxes causes additional financial strain on the state's economy. HD is inherited as an autosomal dominant trait, which means that 50% of the children of an HD patient will inherit the disease and will in turn pass it on to 50% of their children. Individuals diagnosed through genetic testing are at risk of losing insurance coverage in spite of reforms, and can be discriminated against for jobs, school, loans, or other applications. Since there are currently no cures or successful clinical trials to treat HD, many who are at risk are very reluctant to be tested. We are designing trials to treat HD through rescuing neurons in the earlier phases of the disease, before lives are devastated.

Mesenchymal stem cells (MSC) have been shown to have significant effects on restoring synaptic connections between damaged neurons, promoting neurite outgrowth, secreting anti-apoptotic factors in the brain, and regulating inflammation. In addition to many trials that have assessed the safety and efficacy of human MSC delivery to tissues via systemic IV infusion, MSC are also under consideration for treatment of disorders in the CNS, although few MSC clinical trials have started so far with direct delivery to brain or spinal cord tissue. Therefore we are conducting detailed studies in support of clinical trials that will feature MSC implantation into the brain, to deliver the neurotrophic factor BDNF that is lacking in HD. MSC can be transferred from one donor to the next without tissue matching because they shelter themselves from the immune system. We have demonstrated the safe and effective production of engineered molecules from human MSC for at least 18 months, in pre-clinical animal studies, and have shown with our collaborators that delivery of BDNF can have significant effects on reducing disease progression in HD rodent models.

We are developing a therapeutic strategy to treat HD, since the need is so acute. HD patient advocates are admirably among the most vocal in California about their desire for CIRM-funded cures, attending almost every public meeting of the governing board of the California Institute for Regenerative Medicine (CIRM). We are working carefully and intensely toward the planned FDA-approved cellular therapy for HD patients, which could have a major impact on those affected in California. In addition, the methods, preclinical testing models, and clinical trial design that we are developing could have far-reaching impact on the treatment of other neurodegenerative disorders.

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